1636

Atty. Docket No.
182.0001

PATENT

#4
DGJ
5/10/00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: BRANSTROM et al

Continuing Application
To Ser. No.: 08/711,961
filed Sept. 6, 1996 and
CPA filed July 8, 1999

Prior Examiner: Railey, J.

Filed: Concurrently

Prior Group Art Unit 1636

For: BACTERIAL DELIVERY SYSTEM

EXPLANATION UNDER 37. CFR. §1.608(b)

Assistant Commissioner of Patents
Washington, D.C. 20231

Dear Sir:

In connection with the concurrent filing of the accompanying continuing application under 37 C.F.R. §1.53 which along with its preliminary amendment is intended to provoke an Interference based on PRIORITY OF INVENTION and DERIVATION between it and Powell et al US 5,877,159 issued March 2, 1999 (Exhibit 1).[1]

Applicants believe that they are entitled to a holding of *prima facie* priority and a finding of derivation based on the showing made herein.

The present application is a continuation application claiming priority to Serial Number 08/523,855 filed September 6, 1995, now U.S. Patent 5,824,538 issued

[1] All Exhibits are attached to the accompanying Declaration of Maurice U. Cahn.

October 20, 1998 (Exhibit 2), and pending application Serial No. 08/711,961, filed Sept. 6, 1996.

In brief, Applicants previously issued '538 patent is directed to a method of delivering DNA to a cell using attenuated *Shigella* which corresponded to the Group V invention identified in a 10-way restriction requirement issued pursuant to the original application. The restriction requirement identified multiple patentably distinct species including groups specifically directed to the Attenuated *Shigella* Strain, per se and methods for its production, vaccines comprising attenuated *Shigella*, method of reducing disease symptoms by administering Attenuated *Shigella* strain, method of detecting *Shigella* infection. (*See* Restriction Requirement dated October 6, 1996, Exhibit 3.)

Before the issuance of U.S. 5,824,538, Applicants caused the filing of a continuation application. That application was also subject to a multi-invention restriction requirement and the claims directed to directing DNA into to a cell using attenuated *Shigella* were further pursued. That application is currently pending but stands rejected under 35 U.S.C. §102 as being fully anticipated by Powell et al. '159, the patent subject to this request for an interference.

During prosecution, the Powell et al. '159 patent was not subject to restriction as it defined only methods for using bacteria containing a eukaryotic expression cassette encoding a gene, where the gene encodes a vaccine antigen. The patent is classified in Class 514, subclass 44, which corresponds to the same class as Applicants' group V invention of the original restriction requirement (which is the same class that Applicants' '538 patent is classified). Furthermore, in respect to the Group X invention, original claim 44, it was classified in class 435, subclass 252.3 as being "drawn to a method of

delivering functional nucleic acids into a cell using bacteria." Notably, this method corresponds almost precisely to the stated objectives in the Powell et al. '159 patent:

> An object of the present invention is to use live invasive bacteria to deliver one or more eukaryotic expression cassettes to animal cells or animal tissue.
>
> Another object of the present invention is to use live invasive bacteria to deliver one or more eukaryotic expression cassettes encoding a vaccine antigen(s) to animal cells or animal tissue.
>
> Another object of the present invention is to use live invasive bacteria to deliver one or more eukaryotic expression cassettes encoding therapeutic agents to animal cells or animal tissue.
>
> Yet another objective of the present invention is to use live invasive bacteria to deliver one or more eukaryotic expression cassettes encoding biologically active RNA species to animal cells or animal tissue.

Assuming that Applicants' evidence is sufficient to establish a *prima facie* case of priority and derivation, Applicants submit that the evidence contained within the file histories of the subject patents and applications recite interfering subject matter.

For its proof of priority and derivation, Applicants first rely on the written record presented with the recently filed Declaration under Rule 131, by Donata Sizemore, one of the inventors herein (Exhibit 4). That record constitutes the July 1995 governmental Invention Disclosure form that, itself, admittedly post-dates the filing of the Powell application, but also identifies the existence of inventive activity dating back into 1993. Even more significantly, that governmental form in the section entitled "Use Sale or Publication" specifies that "Access made available to Dr. David Hone for purposes of collaboration." Dr. Hone is from the University of Maryland, and one of the co-inventors listed on the Powell et al. '159 patent.

That document also specifies a number of dates relating to the creation of the attenuated *Shigella flexneri Δasd* mutant, the very same mutant described in detail by Powell et al. '159, for example, in reference to Figures 3A ,3B and 4 as well as Examples 4 and 6 of the patent.

One result of providing Dr. Hone with access to and conferring about the invention, the two groups of inventors agreed to jointly submit for publication (to

Science) their respective papers regarding their work. A copy of the Branstrom et al. manuscript is attached hereto as Exhibit 5. This was done to the extent of submitting both of the papers in a single envelope on June 7, 1995. It was the Branstrom et al. paper that was published and the Powell et al. that was rejected. That paper was published in the October 1995 issue of *Science* (Exhibit 6).

Applicants claim to priority for the invention at issue is based on the following evidence attached to the Declaration of Maurice U. Cahn attached hereto, which includes 1) the WRAIR Invention Disclosure Summary and attached six page invention disclosure dated June 30 and July 5, 1995 which details the evolution of the invention subject to the instant application (Exhibit 7). Applicant's also rely on the redacted copies of Drs. Sizemore's and Branstrom's laboratory notebooks attached hereto as Exhibits 8 and 9. Excepting two selected date entries (on page 13 of Exhibit 8 and page 14 of Exhibit 9) respectively referring to dates, November 28, 1994 and April 3, 1995, both of which predate the Powell et al. '159 application filing date of May 6, 1996, the dates have been redacted from the attached copies of those notebook entry pages.

In reference to the development of interfering subject matter Exhibit 8 address the microbiological/animal testing research relating to the development of bacterial strains including the *Shigella Flexneri Δasd* for practice of the invention. Exhibit 9, the Branstrom Notebook selection clearly identify a project entitled "Vaccines" the orientation of which is genetic. That research details the genetic structure of the bacterial genetic mutations including the construction of suicide vectors, the recognition of Shigella serving as carrier of foreign DNA and the capacity for invasiveness. That notebook contains a substantial recitation addressing the efforts leading to both the original Branstrom patent application filed in September 1995 and the *Science* article published in October 1995. Because the two notebooks contain dates preceding the

filing date of the Powell et al. application, Applicants submit that they are entitled to priority and or a declaration of interference between the instant application and the Powell et al.'s US Patent 5,877,159.

Moving to support of the claims and counts as presented in the preliminary amendment, applicant submits that in the context of the expression "eukaryotic expression cassette" a person of ordinary skill in the art would recognize that the expression can be replaced with the more common, and somewhat broader term "vector". For that reason and in that context, claims 45-55 are supported by the pending application specification.

In connection with the support in Applicant's specification to meet the respective following claims and counts including Applicants' original claim 44, a modified version of Powell et al. '159 claim 15 and claim 15 , itself.

Claims' Support

The claims presented by Applicants in their original filings are believed to be fully supported by the specification. Therefore, for the purposes of this explanation, Applicants only detail herein the support for the claims and proposed counts presented in the Preliminary amendment.

Claim 45 presented in the Preliminary Amendment is a copy of Powell et al '159 Claim 1:

> A method for introducing and expressing a gene in animal cells comprising infecting said animal cells with live invasive bacteria, wherein said bacteria contain a eukaryotic expression cassette encoding said gene, wherein said gene encodes a vaccine antigen, wherein said vaccine antigen is expressed at detectable levels, and wherein said animals cells are cultured in vitro.

Applicants turn to the following passages in their specification to provide support for entry of that claim:

Page 2

The bacterial delivery system of the present invention is designed to deliver functional nucleic acids which direct eukaryotic cells to produce antigens and other functional molecules. In this case, toxicity to the carrier is eliminated because plasmid-encoded gene expression is dependent upon the machinery of the eukaryotic cell allowing proper folding of the antigen for presentation or direction of cell functions.

Page 14-15

In another embodiment, the present invention relates to a method for the introduction of DNA or antigens of interest into cells *in vitro*. Such a method would comprise introduction of the desired DNA or antigen into attenuated or attenuated/inactivated *Shigella* such that the desired antigens are produced, and administering said *Shigella* to cells. *Shigella* infects several different cells types, such as BHK (baby hamster kidney cells), HeLa (Human cervical epitheloid carcinoma), CaCo-2 (human colonic adenocarcinoma) and therefor is capable of delivering desired DNA or antigens into cells wherein said DNA can be expressed. Cells following DNA delivery can be transplanted for therapeutic purposes, for gene therapy or used as reagents in diagnostic assays.

Page 21

Strain 15D was able to maintain the commercially available eukaryotic expression vector pCMV without antibiotic selection. pCMV expresses *E. coli* -galactosidase under the control of the immediate early promoter and enhancer from the human cytomegalovirus (CMV) in mammalian cells, which permitted us to easily analyze mammalian-mediated gene expression after delivery (MacGregor and Caskey, *Nucl. Acids Res.* (1989) **17**: 2365).

Page 36

Likewise, because no DNA purification is required for this type of DNA vaccination, which is really a live, attenuated bacterial vector, vaccines can be produced for the cost of fermentation, lyophilization and packaging.

Claim 46 presented in the Preliminary Amendment is a copy of Powell et al '159 Claim 5 and reads:

> The method of claim 45, wherein said invasive bacteria is selected from the group consisting of *Shigella spp, Listeria spp., Rickettsia spp* and enteroinvasive *Escherichia coli.*

Support for this claim is found in the specification at:

Page 2

Attenuated or less virulent *Shigella, Salmonella, Listeria*, and other bacteria have been given orally to immunize against subsequent infection with more virulent forms of these bacteria.

Page 3

This invention can be applied to any desired bacteria.

Page 5

In this invention is described an attenuated *Shigella* strain that can deliver functional nucleic acids to cells and deliver heterologous and homologous antigens. Even though a specific bacteria is described herein and is shown to deliver nucleic acids to eukaryotic cells whether the bacteria were alive or inactivated, this invention is applicable to all bacteria and mycobacteria. Plasmids introduced into other cells such as plant cells may also render these cells capable of delivering nucleic acids.

Page 35

We have discovered a novel method for delivering functional DNA inside cells. This method should not be restricted to *Shigella*, since the invasion genes that *Shigella* utilizes can be inserted into other bacteria such as *E. coli* (Sansonetti *et al. Infect. Immun.* (1983) **39**:1392). Likewise, other bacteria such as *Listeria* are able to invade cells and break out of the phagocytic vacuole into the cytoplasm (Portnoy and Jones, *Ann. N.Y. Acad. Sci.* (1994) **730**:15). Although we have no formal proof that release from the phagocytic vacuole into the cell cytoplasm by the bacteria is essential for DNA delivery, preliminary experiments with *Salmonella typhimurium*, an organism that reaches the cytoplasm only with difficulty, suggests this organism is not an efficient DNA delivery vehicle.

Claim 47 presented in the Preliminary Amendment is a copy of Powell et al '159 Claim 6 and reads:

The method of claim 46, wherein said invasive bacteria is attenuated.

Support for this claim is found in the specification at, for example:

Page 4

Therefore, in view of the above, there is a need for a properly attenuated strain of *Shigella* which could serve as a vaccine candidate against *Shigella* infections as well as a bacterial vector for the delivery of heterologous and homologous antigens and for DNA-mediated immunizations, and gene delivery.

Page 35-36

Any bacterial vector DNA delivery system will need to strike a balance between cell invasion with its subsequent reactogenicity and efficiency of delivery. In the case of *Shigella*, the genes responsible for invasion also cause invasion and apoptosis of macrophages followed by inflammation (Zychlinsky *et al. Nature* (1992) **358**:167). We constructed a *Shigella* strain that in the absence of DAP, is unable to survive inside the cell. Determination of the safety of this strain awaits human trials.. ...Likewise, because no DNA purification is required for this type of DNA vaccination, which is really a live, attenuated bacterial vector, vaccines can be produced for the cost of fermentation, lyophilization and packaging.

Claim 48 presented in the Preliminary Amendment closely tracks claim 1 of Powell et al. '159 but substitutes certain expressions for others. Claim 48 is:

A method for introducing genetic material in animal cells comprising introducing to said animal cells live invasive bacteria, wherein said bacteria contain a vector containing said genetic material, wherein said genetic material encodes a vaccine antigen, wherein said vaccine antigen is expressed at detectable levels, and wherein said animals cells are cultured in vitro.

In this "count" the word "gene" is substituted for by the expression "genetic material," the more proper phrase "introducing into" is substituted for "infecting...with," and the broader "vector" is substituted for the more narrow "eukaryotic expression

cassette," Support for this Count corresponds to that identified above in connection with claim 45.

Claim 49 presented in the Preliminary Amendment is a copy of Powell et al. '159 Claim 13[2] which reads:

> A method for introducing and expressing a gene in animal cells comprising infecting said animal cells with live invasive Shigella spp., wherein said Shigella spp. contain a eukaryotic expression cassette encoding said gene, wherein said gene encodes a vaccine antigen, wherein said vaccine antigen is expressed at detectable levels, and wherein said animals cells are cultured in vitro.

In addition to the specification passages recited to support Claim 45, support for this claim is found in the specification at:

Page 4

> Specifically, the attenuated *Shigella* strain of the present invention is capable of delivering functional nucleic acids and serving as a vaccine candidate itself against *Shigella* infections. The attenuated *Shigella* strain of the present invention enters the cell but, once inside the host cell, dies releasing its contents. The attenuated *Shigella* strain described herein is sufficiently attenuated to not cause disease, while still maintaining the ability to enter mammalian cells.

Claim 50 presented in the Preliminary Amendment is a copy of Powell et al. '159 Claim 14 and reads:

> The method of claim 49, wherein said Shigella spp is *Shigella flexneri.*

Support for this claim is found in the specification at, for example:

Page 5

> A mutation in the gene encoding aspartate β-semialdehyde dehydrogenase (ASD) was placed in *Shigella flexneri* 2a strain 2457T for the specific purpose of delivering DNA to mucosal epithelial cells of the gut. This resulted in a strain unable to grow in the absence of diaminopimelate (DAP), an essential peptidoglycan component comprising the cell wall of gram negative bacteria. DAP is

---

[2] Claim 49 differs from claim 45 only to the extent that it specifically identifies *Shigella* as the infection agent.

not present in mammalian tissues, and is therefore unavailable for scavenge by infecting bacteria. This mutant strain of *Shigella* represents a highly attenuated bacterial vector, which is capable of invading mammalian cells and providing protective immunity against strain specific *Shigella* infection, as well as serving as a delivery vehicle for oral and other mucosal DNA immunization and gene therapy strategies.

Page 6

It is yet another object of the invention to provide an attenuated and an attenuated/inactivated strain of S. *flexneri* for use as a vaccine against *S. flexneri* infections.

Still another object of the invention is to provide an attenuated strain of *S. flexneri* which is mutant in the *asd* gene for use as a vaccine against infection by *S. flexneri*, for reducing the symptoms in an individual caused by such an infection, or as a delivery vehicle for heterologous antigens or DNA.

Page 9

Specifically, the present invention describes the construction of an isolate of *Shigella flexneri* containing a deletion in the gene encoding aspartate β-semialdehyde dehydrogenase (ASD), an essential enzyme required for synthesizing the bacterial cell wall constituent diaminopimelic acid (DAP). Without being bound to a theory, this mutant strain retains the ability to enter mammalian cells, but once inside the cell, is not able to replicate due to the absence of DAP which is unavailable for scavenge from mammalian cells and as a result, the bacteria dies, releasing its contents including intact DNA and antigens already present in the bacteria.

Claim 51 presented in the Preliminary Amendment corresponds to Powell et al Claim 13, and reads:

> A method for introducing and expressing genetic material in animal cells comprising introducing to said animal cells live invasive *Shigella*, wherein said *Shigella* contain a vector containing said genetic material, wherein said genetic material encodes a vaccine antigen, wherein said vaccine antigen is expressed at detectable levels, and wherein said animals cells are cultured in vitro.

The modifications to claim 51 vis-à-vis claim 13 correspond to those made in connection with claim 48 vis-à-vis claim 1. Support for this "count" claim is found in the specification at, for example:

Page 6

It is still another object of the present invention to deliver heterologous foreign antigens expressed by the attenuated *Shigella* for the purpose of inducing in an individual an immune response against the foreign antigen or for treatment of a disease wherein said foreign antigen is missing or found in reduced amount.

Pages 15-16

In still another embodiment, the present invention relates to a vaccine against *Shigella* infection. The attenuated *S. flexneri* strain of the present invention can be used as an immunizing agent against *S. flexneri* infection. This strain has been shown to elicit a protective immune response in a guinea pig keratoconjunctivitis animal model. Other *Shigellae* strains can be attenuated

similarly to the *S. flexneri* by introducing a mutation in a *Shigellae* gene as described above such that the resultant *Shigella* enters the cell and subsequently dies. Such a mutation can be in the *asd* gene for example, and the resulting attenuated strains used as a vaccine against infection with the specific serotype of shigellae strain used, for example, *S. boydii, S. dysenteriae, S. flexneri, and S. sonnei.* The attenuated *Shigella* vaccine can be prepared in the form of a mixed vaccine which contains one strain or several different strains of attenuated *Shigella.* Further, the vaccine can include at least one other antigen as long as the added antigen does not interfere with the effectiveness of the attenuated *Shigella* vaccine and the side effects and adverse reactions, if any, are not increased additively or synergistically.

Vaccines are prepared for oral administration, either as liquid solutions or suspensions; solid form suitable for solution in, or suspension in, liquid prior to administration. The preparation may also be emulsified, or the ingredients are often mixed with excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations, nose drops or powders and contain about $10 - 10^{12}$ attenuated and/or attenuated/inactivated *Shigella.* Vaccines can also be in the form of injectables. Suitable excipients would include, for example, saline or buffered saline (pH about 7 to about 8), or other physiologic, isotonic ...

Claim 52 in the preliminary amendment corresponds to claim 22 of Powell et al in as much as it specifically identifies *Shigella flexneri* as the attenuated bacteria. Support for this claim is the same as that recited above in respect to claim 50.

Claim 53 presented in the Preliminary Amendment is a copy of Powell et al '159 Claim 15 which reads:

> A method for inducing an immune response in an animal comprising infecting said animal with attenuated live invasive bacteria, wherein said bacteria contain a eukaryotic expression cassette encoding said gene, wherein said gene encodes a vaccine antigen, wherein said vaccine antigen is expressed at levels sufficient to induce an immune response, wherein said invasive bacteria are administered to a mucosal surface of said animal.

In addition to the specification passages recited to support Claim 45, support for this claim is found in the specification at, for example:

Page 6

> It is still another object of the present invention to deliver heterologous foreign antigens expressed by the attenuated *Shigella* for the purpose of inducing in an individual an immune response against the foreign antigen or for treatment of a disease wherein said foreign antigen is missing or found in reduced amount.

Page 15-16

In still another embodiment, the present invention relates to a vaccine against *Shigella* infection. The attenuated *S. flexneri* strain of the present invention can be used as an immunizing agent against *S. flexneri* infection. This strain has been shown to elicit a protective immune response in a guinea pig keratoconjunctivitis animal model. Other *Shigellae* strains can be attenuated similarly to the *S. flexneri* by introducing a mutation in a *Shigellae* gene as described above such that the resultant *Shigella* enters the cell and subsequently dies. Such a mutation can be in the *asd* gene for example, and the resulting attenuated strains used as a vaccine against infection with the specific serotype of shigellae strain used, for example, *S. boydii, S. dysenteriae, S. flexneri, and S. sonnei.* The attenuated *Shigella* vaccine can be prepared in the form of a mixed vaccine which contains one strain or several different strains of attenuated *Shigella.* Further, the vaccine can include at least one other antigen as long as the added antigen does not interfere with the effectiveness of the attenuated *Shigella* vaccine and the side effects and adverse reactions, if any, are not increased additively or synergistically.

Vaccines are prepared for oral administration, either as liquid solutions or suspensions; solid form suitable for solution in, or suspension in, liquid prior to administration. The preparation may also be emulsified, or the ingredients are often mixed with excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations, nose drops or powders and contain about 10 - 10^{12} attenuated and/or attenuated/inactivated *Shigella.*

Vaccines can also be in the form of injectables. Suitable excipients would include, for example, saline or buffered saline (pH about 7 to about 8), or other physiologic, isotonic ...

Claim 54 is a copy of combined Powell et al. '159 dependant claims 18 and 22 and support therefor is identified in respect to claim 50, *supra*.

Claim 55 is a copy of Powell et al. '159 dependant claim 20. Support for this claim is found in the specification at, for example:

Page 15

The preparation may also be emulsified, or the ingredients are often mixed with excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations, nose drops or powders and contain about 10 - 10^{12} attenuated and/or attenuated/inactivated *Shigella.*

Page 31

The purpose of this experiment was to measure in an alternative model (i.e. murine intranasal) the ability of 15D to deliver DNA *in vivo.* In addition, immune responses to the carrier were also determined.

Claim 56 presented in the Preliminary Amendment and corresponding to Powell et al Claim 15, reads:

A method for inducing an immune response in an animal comprising introducing attenuated live invasive bacteria, wherein said bacteria contain a vector containing genetic material, wherein said genetic material encodes a vaccine antigen, wherein said

vaccine antigen is expressed at levels sufficient to induce an immune response, wherein said invasive bacteria are administered to a mucosal surface of said animal.

The modifications to claim 56 vis-à-vis claim 15 correspond to those made in connection with claim 48 vis-à-vis claim 1 and claim 51 vis-à-vis claim 13. Support for this "count" claim is identified above in respect to claim 53.

Dependant claims 57-59 depend from claim 56 and correspond to and share the same specification support as claims 50/54, 55, and 46.

APPLICANTS' PROPOSED COUNTS

Applicants submit that any or all of the following counts are broad enough to cover the claimed invention of the Powell et al '159 patent and Applicants invention and are fully supported by Applicants' application as detailed above.

COUNT 1 a copy of claim 44 of the pending application:

A method for the delivery of functional nucleic acids into a cell using bacteria comprising:

(i) introducing said nucleic acids into an attenuated bacteria; and

(ii) administering said bacteria to said cell.

COUNT 2 a copy of claim 56 of the Preliminary Amendment of the pending application:

A method for inducing an immune response in an animal comprising introducing attenuated live invasive bacteria, wherein said bacteria contain a vector containing genetic material, wherein said genetic material encodes a vaccine antigen, wherein said vaccine antigen is expressed at levels

sufficient to induce an immune response, wherein said invasive bacteria are administered to a mucosal surface of said animal.

COUNT 3 a copy of claim 53 of the Preliminary Amendment of the pending application which is a copy of Claim 15 of Powell et al '159:

A method for inducing an immune response in an animal comprising infecting said animal with attenuated live invasive bacteria, wherein said bacteria contain a eukaryotic expression cassette encoding said gene, wherein said gene encodes a vaccine antigen, wherein said vaccine antigen is expressed at levels sufficient to induce an immune response, wherein said invasive bacteria are administered to a mucosal surface of said animal.

REMARKS

The invention of this application and the Powell et al. '159 patent both involve methods using invasive bacteria for introducing and expressing genetic material into a cell for purposes including the generation of an immune response. It cannot be disputed that both the application and Powell et al. '159 disclose as the invasive bacteria, attenuated Shigella, and more specifically attenuated Shigella Flexneri as a vehicle to accomplish the claimed method. It also cannot be disputed, based on the documentary evidence attached hereto under the undersigned's declaration, that Applicants have established a *prima facie* conception date prior to the May 1995 filing date of Powell et al. and that Powell et al. at least in part derived part of the subject matter recited in the specification supporting the patent claims invention from Applicants.

In view of the foregoing, Applicants submit that the counts presented herein conform to the rules, the Powell et al '159 patent and Applicants application.

Furthermore, in addition to the claims presented in the Preliminary Amendment, Applicants submit that the subject matter of many of their original claims and particularly, claim 44 recites subject matter that correspond to an effective count for the purposes of declaring an interference.

In view of the foregoing, Applicants believe that they have provided sufficient evidence to provoke an interference between the Powell et al. '159 patent and the instant application and respectfully solicit that an interference be declared.

Respectfully submitted,

CAHN & SAMUELS, LLP

By: _____

Maurice U. Cahn, Esq.
Reg. No. 30,454
2000 P Street, N.W. (Suite 200)
Washington, D.C. 20036
Telephone: (202) 331-8777
Facsimile: (202) 331-3838
February 25, 2000